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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
10/719,990	11/21/2003	Alan Howe	421/73/2	1736	
25297	7590	04/20/2006	EXAMINER		
JENKINS, WILSON, TAYLOR & HUNT, P. A.				FETTEROLF, BRANDON J	
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DURHAM, NC 27707				1642	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,990	HOWE, ALAN	
	Examiner Brandon J. Fetterolf, PhD	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 26 January 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims:

- 4) Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) 15-35 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-14 and 36-38 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____

Response to the Amendment

The Amendment filed on 1/26/2006 in response to the previous Non-Final Office Action (08/29/2005) is acknowledged and has been entered.

Claims 1-38 are currently pending.

Claims 15-35 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-14 and 36-38 are currently pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 1-3, 6-9 and 36-38 remain rejected under 35 U.S.C. 103(a) as being unpatentable over McMahan et al. (Analytical Biochemistry 1996; 236: 101-106) or Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001) in view of Neville et al. (Protein Science 1997; 6: 2436-2445) and Nieba et al. (Analytical Biochemistry 1997; 252: 217-228).

McMahan et al. disclose a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (abstract, lines 5-7) that the chelator is nitriloacetic acid and the metal is Ni^{2+} . With regards to the detectable moiety, McMahan et al. teach (abstract, lines 8-9) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan et al. teach that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label (page 103, Fig. 1). The reference further teaches that the conjugate is soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column).

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+} . With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference

further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit.

Neither McMahan et al. nor Molecular Probes teach that the metal ion is either Ga³⁺ or Fe³⁺.

Nieba et al. teaches that while typically the metals Ni²⁺, Zn²⁺, Co²⁺, and Cu²⁺ are chelated to NTA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teach that Fe³⁺ loaded NTA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides (abstract).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute a metal ion such as Ga³⁺ or Fe³⁺ as taught by Neville et al. in view of Nieba et al. One would have been motivated to do so because as taught by Nieba et al., the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag. For example, Neville et al. teaches that Fe³⁺ loaded NTA and IDA metal-ion affinity resin preferentially bound to phosphoproteins as compared to His-containing peptides. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by McMahan et al. or Molecular Probes in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins, such as phosphoproteins, which do not contain a His tag.

In response to this rejection, Applicants contend that the Patent Office appears to be interpreting Nieba to suggest that the disclosure related to metal ion optimization relates broadly to metal ions other than Ni²⁺, Zn²⁺, Co²⁺ and Cu²⁺ and to application other than binding to His tags. However, Applicants submit that there is no support in the Nieba reference for such a broad interpretation because Nieba relates only to optimization of binding conditions between Ni²⁺-NTA and a His tag. For Example, Applicants assert that every protein for which binding was desired in Nieba contained a His tag, and every conjugate tested was a Ni²⁺-NTA conjugate. Moreover, Applicants respectfully submit that there is no disclosure in Nieba that other metals can be used positively to selectively bind any protein that does not have a His tag. Accordingly, Applicants argue that when read in its entirety and in context, Nieba teaches no more than a general approach to

maximizing the binding of an Ni^{2+} -NTA conjugate to His tagged proteins while minimizing the binding of non-tagged proteins to the same Ni^{2+} NTA conjugate. Thus, Applicants submit that one of ordinary skill in the art would not have been motivated to combine Neville in view of Nieba with McMahan or the Pro-QTM Product Information to produce the phosphoprotein detection agent as claimed.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertion that Nieba relates, in its entirety to Ni^{2+} -NTA and a His tag, the Examiner acknowledges that Nieba teaches BIACORE analysis of histidine-tagged protein using a chelating NTA sensor chip. However, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is **some** teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. (*Emphasis added*) See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Nieba suggests the motivation to optimize and/or substitute the metal ion in immobilized metal affinity chromatography, whereas Neville et al. teaches that Fe^{3+} loaded NTA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides. For example, Nieba et al. teaches on page 217, 2nd column, 1st paragraph: “Typically Ni^{2+} , Zn^{2+} , Co^{2+} , and Cu^{2+} chelated to IDA or NTA have been used in chromatographic media for immobilized metal affinity chromatography (IMAC). The choice of the metal ion and buffer conditions for IMAC are optimized for the highest selectively to other proteins not carrying a His tag,” (*Emphasis added*). Furthermore, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the references represent analogous teachings of an affinity chromatography. As such, one of skill in the art would have a reasonable expectation of success that

by substituting the metal ion as taught by McMahan et al. or Molecular Probes in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins, such as phosphoproteins, which do not contain a His tag.

Claims 1-2, 4 and 6-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona) in view of Neville et al. (Protein Science 1997; 6: 2436-2445) and Nieba et al. (Analytical Biochemistry 1997; 252: 217-228).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety via a PEG spacer group. With regards to the chelator-metal moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu²⁺. With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. The reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract, page 20)

Ehtashami does not explicitly teach the metal ion is either Ga³⁺ or Fe³⁺.

Nieba et al. teaches that while typically the metals Ni²⁺, Zn²⁺, Co²⁺, and Cu²⁺ are chelated to IDA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teach that Fe³⁺ loaded IDA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides (abstract).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute a metal ion such as Ga³⁺ or Fe³⁺ as taught by Neville et al. in view of Nieba et al. One would have been motivated to do so because as taught by Nieba et al., the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His

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tag. For example, Neville et al. teaches that Fe^{3+} loaded NTA and IDA metal-ion affinity resin preferentially bind to phosphoproteins as compared to His-containing peptides. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by Ehteshami et al. in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins, such as phosphoproteins, which do not contain a His tag.

In response to this rejection, Applicants contend that one of ordinary skill in the art would not have been motivated to combine Neville and Nieba because the Patent Office's assertions with respect to the disclosure of Nieba are based on an impermissibly broad reading of Nieba as discussed above. Moreover, Applicants assert that that Ehteshami appears to disclose a biotin-PEG-iminodiacetic acid-copper conjugate for purifying avidin. Moreover, Applicants assert that as shown in Figure 1.2 of Ehteshami, a chelating matrix coordinating a metal ion is bound to a solid support, wherein the metal ion is also coordinated by a PEG derivative comprising a "bioligand". As such, Applicants argue that this biotin/bioligand moiety functions in the disclosed PEG derivatives as the ligand that binds to the chelating matrix attached to the solid support; and therefore, in the heterobifunctional polyethylene glycols disclosed by Ehteshami, the chelator-metal ion moiety binds to the PEG derivatives. In contrast, Applicants contend that the function of the chelator-metal ion moiety present in the phosphoprotein detection reagent (PPDR) of claim 1, which clearly recites that the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein. Thus, Applicants assert that even if one of ordinary skill in the art were motivated to replace the copper ion in the heterobifunctional polyethylene glycols disclosed in Ehteshami et al. with Ga^{3+} or Fe^{3+} , the resulting chelator-metal ion moieties would still bind to the PEG derivative.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants arguments pertaining to the lack of motivation to combine Neville and Nieba, the Examiner recognizes that Nieba suggests the motivation to optimize and/or substitute the metal ion in immobilized metal affinity chromatography, whereas Neville et al. teaches that Fe^{3+} loaded NTA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides. As such, these arguments have not been found persuasive for reasons set forth above. Regarding Applicants contention that Ehteshami's biotin/bioligand moiety, as shown in Figure 1.2, functions in the disclosed PEG derivatives as the ligand that binds to the chelating matrix

attached to the solid support, wherein the chelator-metal ion moiety binds to the PEG derivatives, the Examiner acknowledges and agrees with Applicants interpretation of the results shown in Figure 1.2. However, the Examiner recognizes that Ehteshami also discloses the use of the heterobifunctional bispecific chelate polymer in protein purification and characterization using a two phase aqueous system, wherein one of the heterobifunctional bispecific chelate polymers is biotin-PEG-IDA-Cu(II) (page 123, Chapter 5 and page 128, last paragraph). For example, Ehteshami teaches that aqueous two-phase partitioning in conjunction with metal affinity and specific affinity partitioning using heterobifunctional affinity polymers can be used as tool for distinguishing and screening of the specific binding sites on the surface of the proteins (page 145, 2nd paragraph). As such, it appears that the prior arts heterobifunctional bispecific chelate polymer has the same function as the instantly claimed phosphoprotein detection reagent recited in claim 1.

Therefore, No claim is allowed.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER